

## **R E M A R K S**

Claims 275, 296 and 297 are pending in the above-referenced application.

### **1. The Rejections Under 35 USC §102**

Two rejections were made under 35 USC §102. These are discussed in detail below.

#### **A. The Rejection Over Engelhardt et al.**

Claims 275 and 296 are rejected under 35 U.S.C. §102(b) as being anticipated by Engelhardt et al. (US 5,260,433) (hereinafter “Engelhardt”). The Office Action specifically states:

The claims are drawn to a multimeric composition comprising more than one monomeric unit, wherein each monomeric unit comprises a protein ligand to a cell surface receptor and a single-stranded polynucleotide, wherein the single-stranded polynucleotide is attached via hydrogen bonding to a complementary single-stranded polynucleotide, wherein the cell surface receptor is a hormone receptor or the ligand is a hormone.

Engelhardt et al. teach a multimeric composition comprising multiple protein ligands covalently attached or bound to a single-stranded polynucleotide or a double-stranded polynucleotide of A:U comprising a single-stranded poly A nucleotide and a single-stranded poly U nucleotide, wherein the protein ligands bind to their cognate protein receptors such as hormone receptors. See columns 26-28. Accordingly, all claim limitations are taught by Engelhardt et al.

Applicants traverse the rejection for the following reasons. An essential element that is lacking in Engelhardt is the presence of proteins that are covalently bound to a nucleic acid. Covalent attachment is discussed in the context of Sig being joined to a base (B), sugar (S) or phosphate (P) moiety. However, rather than proteins ligands being attached, the Engelhardt patent restricts itself to labeling nucleic acids with small molecules (ligands) that

proteins may bind to. The only proteins that are disclosed as possible Sig moieties are disclosed in column 24, lines 25-30 as comprising

an enzyme or enzymic material, such as alkaline phosphatase, glucose oxidase, horseradish peroxidase, ribonuclease, acid phosphatase or beta-galactosidase

These proteins clearly are not ligands that bind to cell surface receptors.

In column 24, lines 45-49, the Sig moiety is further defined as follows:

Most usefully, the Sig moiety is a polysaccharide or oligosaccharide or monosaccharide, which is capable of complexing with or being attached to a sugar or polysaccharide binding protein such as a lectin, e.g. Concanavalin A.

The binding of a protein to its appropriate ligand on the nucleic acid takes place through **non-covalent** means. For instance, in column 26, lines 13-16 of Engelhardt, the specification states

The detection of nucleic acids to which specific molecules have been covalently attached can be effected through the use of many naturally occurring proteins to which small molecules are known to specifically bind.

Later in column 26, a list of compounds and their binding partners is provided (lines 27-60). Even when discussing ligands to a cell surface receptor (lines 44-46) the ligands are referred to as small organic molecules and not proteins:

Hormone receptors and other receptors on the surface of a cell to which small organic molecules will bind.

In this context, the small molecule is the ligand covalently attached to a nucleic acid and a receptor (a protein) binds to it non-covalently to generate a signal. Thus, the ligands disclosed in Engelhardt are small molecules not protein ligands.

Applicants further note that it is stated in the Engelhardt patent, column 28, lines 7-10 that

Additionally, the nucleotides and polynucleotides are prepared in accordance with this invention to provide a

**ligand**, such as the component Sig, **to which specific peptides can combine**....

thus again describing a situation where peptides (proteins) are binding to the ligands present on the nucleic acids.

Further, Applicants respectfully that the description of an A:U double-stranded polynucleotide with a protein ligand binding to a protein receptor on page 3 of the Office Action is inaccurate. There is no disclosure regarding attaching a protein ligand to either the A or U strand. It is only disclosed that modified nucleotides containing the Sig moiety could be incorporated.

In summary, as discussed above, there are no protein ligands described in the Engelhardt patent. Only proteins that bind to a ligand that is a polysaccharide or small molecules are described.

Applicants further assert that claim 296 would also not be anticipated by Engelhardt. This is because claim 296 depends from claim 275. Thus, arguments made with respect to claim 275 would apply to claim 275 as well. Further, as noted above, there is no disclosure of a hormone covalently attached to a single-stranded polynucleotide. The hormone receptor protein in Engelhardt binds to a small molecule ligand.

In view of the above arguments, Applicants assert that the rejection over Englehardt has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

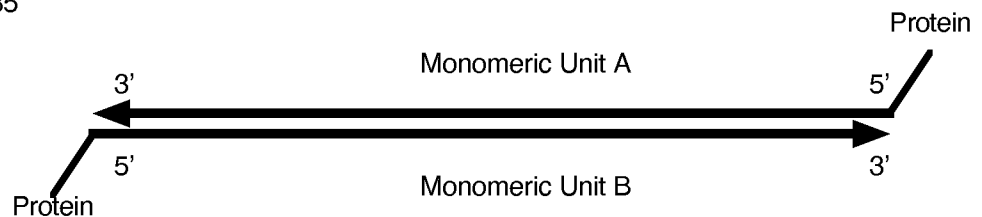
#### **B. Myers et al.**

Claim 275 has been rejected as being anticipated over Myers. The Office Action specifically states:

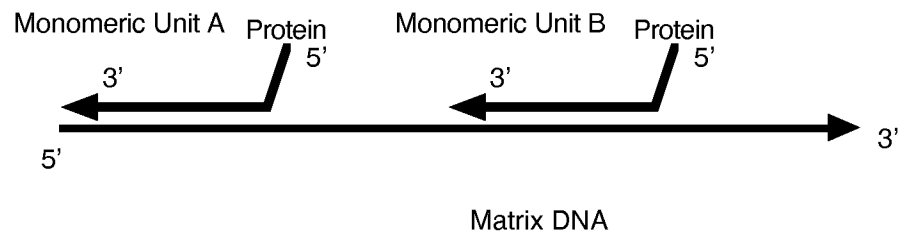
Myers teaches a multimeric compound comprising a double-stranded polynucleotide attached to EGF molecules, wherein the double-stranded polynucleotide comprises two independent complementary single-stranded polynucleotides. See the entire reference. Hence, all claim limitations are taught by Myers.

Applicants respectfully traverse the rejection. The structure taught in Myers is different from the structure of the present invention. As stated in the Office Action, there is a covalent attachment of a single EGF molecule to the 5' end of a nucleic acid strand. As seen in Figure 2 of the Myers reference, this is not a multimer of proteins but rather a single protein attached to a single nucleic acid. Even assuming that the presence of a Bam H1 site at each end of the fragment implies that EGF can potentially be attached to the 5' end of each strand, the structure would not meet the limitations of claim 275. To assist in visualization of the difference between the Myers reference and the present invention a diagram is provided below.

EP 0273085



Present Invention



In this diagram, the Myers monomeric units (A and B) each consists of a nucleic acid (the second element) covalently attached to a protein (EGF) that is a ligand to a cellular receptor (the first element). However, claim 275 recites that the second element of **each** monomeric unit is hydrogen bonded to **a** polynucleotide matrix. In contrast, the Myers monomeric units (A and B) are hybridized to each other rather than to a common matrix polynucleotide. In contrast, the illustration of the present invention shows that each of the multimeric units (A and B) fulfills the requirement “wherein each monomeric unit

is attached to a binding matrix". The illustration above is also a condensed version of Figures 22 and 23 from the present application. Thus, clearly, not all of the limitations of claim 275 is not met.

In view of the above arguments, Applicants assert that the rejection over Myers has been overcome. Therefore, Applicants respectfully request that the rejection over Myers be withdrawn.

## **2. The Rejection Under 35 USC 103**

Claims 275 and 296-297 are rejected under 35 U.S.C. §103(a) as being unpatentable over Engelhardt et al. (US 5,260,433, applicant's citation) in view of Osborne et al. (*PNAS*, 1976, 73 :4536-4540). The Office Action specifically states:

Engelhardt et al. teach a multimeric composition comprising multiple protein ligands covalently attached or bound to a single-stranded polynucleotide or a double-stranded polynucleotide of A:U comprising a single-stranded poly A nucleotide and a single-stranded poly U nucleotide, wherein the protein ligands bind to their cognate protein receptors such as hormone receptors. See columns 26-28. Engelhardt et al. do not teach that the hormone receptor is insulin receptor or that the hormone ligand is insulin.

Osborne et al. teach that insulin, glucocorticoids, prolactin, and estrogen are hormones and that insulin interacts specifically with its receptor, insulin receptor, to simulate growth in human breast cancer cell lines. See the entire reference.

It is concluded in the Office Action that

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have insulin in place of the generic protein hormone ligands of Engelhardt et al.

One of ordinary skill in the art would have been motivated to do so because only countable number of protein hormone ligand species were known in the art including insulin at the time of the invention as taught by Osborne et al., and because the structure of a multimeric compounds

comprising two complementary polynucleotides to which protein hormone ligands are covalently attached was known in the art as taught by Engelhardt et al. Hence, the ordinary skilled artisan would have had made, with a reasonable expectation of success, a multimeric composition comprising multiple insulin ligands covalently attached to a double-stranded polynucleotide at the time of the invention. Accordingly, the claimed invention taken as a whole would have been prima facie obvious at the time of filing.

Applicants traverse the rejection. First, Applicants question whether there would have been motivation to apply the teachings of Engelhardt to the method of Osborne to obtain the compositions of the present invention as asserted in the Office Action. The disclosure of Engelhardt of “two complementary oligonucleotides polynucleotides to which protein hormone ligands are covalently attached” does not seem relevant to the present claims for two reasons. First, no protein hormones are described in Engelhardt; this reference only discloses small organic molecules that bind to hormone receptors. Second, the multimeric subunits are not supposed to be complementary to each other but to a common single-stranded polynucleotide matrix. Osborne would not add much to the disclosures of Engelhardt since Osborne only discloses that insulin binds to insulin receptors.

Furthermore, the motivation for Engelhardt to supply multiple copies of his “SIG” is for the purpose of increasing the amount of signal detected when trying to detect the presence or numbers of copies of an analyte of interest. With regard to Engelhardt’s use of A:U, this seems to be for the purpose of stimulating an immune response. Modifications are actually made to A:U for the purpose of protecting the polynucleotides from nuclease action and increasing induction of interferon. Neither purpose is suitable for the use of insulin as taught by Osborne. The essence of the Osborne paper is a description of a cell line that has insulin receptors such that responses can be measured after in vitro administration of insulin to the cell culture. No particular merit is described for having multimerized versions of insulin nor is any particular need described. The

particular cell line of the Osborne reference may have utility in testing the effects of compositions described in the present invention but in itself provides no motivation to obtain multimerized insulin. Thus, one of ordinary skill in the art would not have been motivated to combine the cited references.

Even assuming *arguendo* that there would have been motivation, one would not have obtained the claimed multimeric composition. This is because as noted in the previous section, there is no teaching in Engelhardt regarding a composition containing (a) a monomeric unit containing a protein ligand to a cell surface protein that is covalently attached to a single stranded polynucleotide and (b) a binding matrix comprising a complementary polynucleotide. Only a small molecule ligand is covalently attached to the polynucleotide. Thus, at best the combination of Engelhardt and Osborne would be a polynucleotide covalently attached to a small molecule which could bind to an insulin receptor.

In view of the above arguments, Applicants assert that the rejection under 35 USC 103 has been overcome. Therefore, Applicants respectfully request that the rejection be withdrawn.

### **3. Summary and Conclusions**

It is Applicants belief that the pending claims are in condition for allowance. If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Date: June 30, 2009

Respectfully submitted,  
/Cheryl H Agris/  
Cheryl H. Agris, Reg. No. 34,086